

We claim:

1. A process for the production of atorvastatin calcium in amorphous form comprising:
 - a) reacting a solution of (4*R*-cis)-1,1-dimethylethyl-6-{2-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1*H*-pyrrol-1yl]ethyl}-2,2-dimethyl-1,3-dioxane-4-acetate (Compound H) in a water-miscible solvent with an acid to obtain [*R*-(*R*^{*},*R*^{*})]-1,1-dimethylethyl-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1*H*-pyrrole-1-heptanoate (Compound I);
 - b) treating Compound I with an alkali metal hydroxide to obtain an alkali metal salt of atorvastatin;
 - c) washing the solution of alkali metal salt of atorvastatin with a solvent immiscible or slightly miscible in water;
 - d) treating the washed solution of alkali metal salt of atorvastatin with a calcium salt or calcium hydroxide to obtain atorvastatin calcium;
 - e) isolating crude atorvastatin calcium;
 - f) purifying crude atorvastatin calcium by dissolving in a mixture of tetrahydrofuran and methanol, and precipitating with water to obtain pure atorvastatin calcium in crystalline form; and
 - g) converting crystalline pure atorvastatin calcium so obtained into amorphous form.
2. A process for purifying atorvastatin calcium comprising dissolving crude atorvastatin calcium in a mixture of tetrahydrofuran and methanol, and precipitating with water to obtain pure atorvastatin calcium in crystalline form.
3. The process of claim 2, wherein the acid used is an inorganic acid.

- 1 4. The process of claim 3, wherein the acid is selected from the group consisting of
2 hydrochloric, hydrobromic, sulphuric, phosphoric and nitric acids.
- 1 5. The process of claim 1, wherein the water-miscible solvent is selected from the
2 group consisting of acetonitrile, alcohols, cyclic ethers, ketones and mixtures
3 thereof.
- 1 6. The process of claim 5, wherein alcohols are selected from the group consisting of
2 methanol, ethanol, propanol, and isopropanol.
- 1 7. The process of claim 1, wherein the reaction of step b) is carried out at a pH of
2 about 12.
- 1 8. The process of claim 1, wherein the alkali metal hydroxide is selected from the
2 group consisting of sodium hydroxide, potassium hydroxide and lithium
3 hydroxide.
- 1 9. The process of claim 1, wherein the solvent immiscible or slightly miscible in
2 water is selected from the group consisting of ethers, esters, and hydrocarbons.
- 1 10. The process of claim 9, wherein ethers are selected from the group consisting of
2 methyl tertiary butyl ether, diethyl ether, methyl ethyl ether and dibutyl ether.
- 1 11. The process of claim 1, wherein the pH of the solution of step c) is lowered to
2 about 7.8 to 8.2 with an acid before proceeding with step d).
- 1 12. The process of claim 1, wherein step d) is performed at a temperature of about 45
2 to 55 °C.
- 1 13. The process of claim 1, wherein the calcium salt is selected from the group
2 consisting of calcium acetate, calcium chloride, calcium sulfate, calcium nitrate
3 and calcium phosphate.
- 1 14. The process of claim 1, wherein any residual solvent immiscible or slightly
2 miscible in water remaining in the reaction mixture is removed after step d) is
3 removed under reduced pressure.
- 1 15. The process of claim 1, wherein crude atorvastatin calcium is precipitated by
2 addition of water.

- 1 16. The process of claim 15, wherein water is added at a temperature of about 55 to
2 65°C.
- 1 17. The process of claim 1, 15 or 16, wherein seeds of crystalline atorvastatin calcium
2 are added to the reaction mixture.
- 1 18. The process of claim 1, or 15 to 17, wherein crude atorvastatin calcium is isolated
2 by cooling the reaction mixture to a temperature of about 20 to 35 °C.
- 1 19. The process of claim 1 or 2, wherein tetrahydrofuran, methanol and water are in
2 the volume ratio 1:1:4.
- 1 20. The process of claim 1, 2 or 19, wherein water is added at a temperature of about
2 60 to 65 °C.
- 1 21. The process of claims 1, 2, 19 or 20, wherein seeds of crystalline atorvastatin
2 calcium are added to facilitate the precipitation.
- 1 22. The process of claim 21, wherein seeds of crystalline atorvastatin calcium are
2 added at a temperature of about 50 °C.
- 1 23. The process of claims 1, or 19 to 22, wherein pure atorvastatin calcium is isolated
2 by cooling the mixture to a temperature of about 30 to 35 °C.
- 1 24. The process of claim 1, which comprises an additional step wherein the pure
2 crystalline atorvastatin calcium obtained after step f) is suspended in a mixture of
3 methanol and water in the volume ratio 1 to 5 and stirred with seed crystals of
4 crystalline form I, to obtain atorvastatin calcium in crystalline form I.
- 1 25. The process of claim 24, wherein the stirring is performed at a temperature of
2 about 30 to 45°C.
- 1 26. The process of claim 1, which comprises an additional step wherein the pure
2 crystalline atorvastatin calcium obtained after step f) is suspended in 15 to 25
3 volumes (w.r.t weight of atorvastatin calcium) of a mixture of methanol and water
4 in the volume ratio 3 to 2 and stirred with seed crystals of crystalline form II, to
5 obtain atorvastatin calcium in crystalline form II.

- 1 27. The process of claim 24, which comprises a further additional step wherein the
2 obtained crystalline form I of atorvastatin calcium is suspended in 15 to 25
3 volumes (w.r.t weight of atorvastatin calcium) of a mixture of methanol and water
4 in the volume ratio 3 to 2 and stirred with seed crystals of crystalline form II, to
5 obtain atorvastatin calcium in crystalline form II.
- 1 28. The process of claim 26 or 27, wherein the stirring is performed at a temperature of
2 about 10 to 65 °C.
- 1 29. The process of claim 1, wherein amorphous atorvastatin calcium is obtained by
2 dissolving pure crystalline atorvastatin calcium in tetrahydrofuran and adding the
3 resulting solution to cyclohexane.
- 1 30. The process of claim 29, wherein water is added to tetrahydrofuran to dissolve
2 pure crystalline atorvastatin calcium.
- 1 31. A process for the production of stabilized, amorphous atorvastatin calcium
2 comprising:
- 3 a) dissolving crystalline atorvastatin calcium and an antioxidant in a solvent;
4 b) adding the atorvastatin calcium and antioxidant solution to an antisolvent;
5 and
6 c) separating precipitated, amorphous atorvastatin calcium from the resulting
7 suspension to obtain stabilized, amorphous atorvastatin calcium.
- 1 32. A process for the production of atorvastatin calcium in amorphous form
2 comprising:
- 3 a) dissolving crystalline atorvastatin calcium in a hydroxylic solvent;
4 b) adding the obtained solution of atorvastatin calcium to a non-hydroxylic
5 anti-solvent, wherein the non-hydroxylic anti-solvent has a higher boiling
6 point than the hydroxylic solvent;
7 c) concentrating the solution so obtained to remove the hydroxylic solvent;
8 and
9 d) separating precipitated amorphous atorvastatin calcium from the resulting
10 suspension to obtain amorphous atorvastatin calcium.

- 1 33. The process of claim 32, wherein an antioxidant is added to the solution of
2 atorvastatin calcium in hydroxylic solvent.
- 1 34. The process of claim 31 or 33, wherein the antioxidant is selected from the group
2 consisting of butylated hydroxyanisole, butylated hydroxytoluene and tertiary-
3 butylated hydroquinone.
- 1 35. The process of claim 1, wherein the conversion to amorphous form is achieved
2 according to the process of claim 31, 32 or 33.
- 1 36. The process of claim 30 to 33, wherein the solution of atorvastatin calcium is dried
2 before precipitation of amorphous atorvastatin calcium.
- 1 37. The process of claim 36, wherein the solution is filtered through dry molecular
2 sieves.
- 1 38. The process of claim 36, wherein the solution is made using excess of solvent,
2 which is then concentrated to achieve drying.
- 1 39. The process of claim 31, wherein the solvent is selected from the group consisting
2 of ketones, esters, chlorinated hydrocarbons, cyclic ethers, alcohols, nitriles,
3 dipolar aprotic solvents, and mixtures thereof with water.
- 1 40. The process of claim 39, wherein the cyclic ethers are selected from the group
2 consisting of dioxan, tetrahydrofuran, and mixtures thereof.
- 1 41. The process of claim 31, wherein the anti-solvent is selected from the group
2 consisting of hydrocarbons and dialkyl ethers.
- 1 42. The process of claim 32, wherein the hydroxylic solvent is selected from the group
2 consisting of alcohols, and mixtures thereof with water.
- 1 43. The process of claim 39 or 42, wherein alcohols are selected from the group
2 consisting of methanol, ethanol, propanol, and isopropanol.
- 1 44. The process of claim 32, wherein the non-hydroxylic anti-solvent is selected from
2 the group consisting of hydrocarbons and dialkyl ethers.
- 1 45. The process of claim 41 or 44, wherein the hydrocarbons are selected from the
2 group consisting of cyclohexane, hexane, heptane, petroleum ethers, toluene, and
3 xylene.

- 1 46. The process of claim 1, wherein (4*R-cis*)-1,1-dimethylethyl-6-{2-[2-(4-
2 fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1*H*-pyrrol-
3 1yl]ethyl}-2,2-dimethyl-1,3-dioxane-4-acetate (Compound H) is obtained by
- 4 a) treating (*R*)-ethyl 4-cyano-3-hydroxybutanoate (Compound A) with 1,1-
5 dimethylethylacetate (Compound B), in the presence of n-butyl lithium and
6 diisopropyl amine to obtain (*R*)-1,1-dimethylethyl-6-cyano-5-hydroxy-3-
7 oxohexanoate (Compound C),
- 8 b) treating Compound C with diethyl methoxyborane and sodium borohydride
9 to obtain [*R*-(*R**,*R**)]-1,1-dimethylethyl-6-cyano-3,5-dihydroxyhexanoate
10 (Compound D),
- 11 c) treating Compound D with 2,2-dimethoxy propane and methanesulfonic
12 acid to obtain (4*R-cis*)-1,1-dimethylethyl-[6-cyanomethyl-2,2-dimethyl-1,3-
13 dioxan]-4-acetate (Compound E),
- 14 d) treating Compound E under reducing conditions to obtain (4*R-cis*)-1,1-
15 dimethylethyl-[6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl] acetate
16 (Compound F), and
- 17 e) condensing Compound F with (±)-4-fluoro-α-(2-methyl-1-oxopropyl)-γ-
18 oxo-*N*,β-diphenylbenzenebutaneamide (Compound G) to obtain (4*R-cis*)-1,1-
19 dimethylethyl-6-{2-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-
20 (phenylamino)carbonyl]-1*H*-pyrrol-1yl]ethyl}-2,2-dimethyl-1,3-dioxane-4-acetate
21 (Compound H).
- 1 47. A process for the production of atorvastatin calcium in amorphous form, as herein
2 described and exemplified by the examples.